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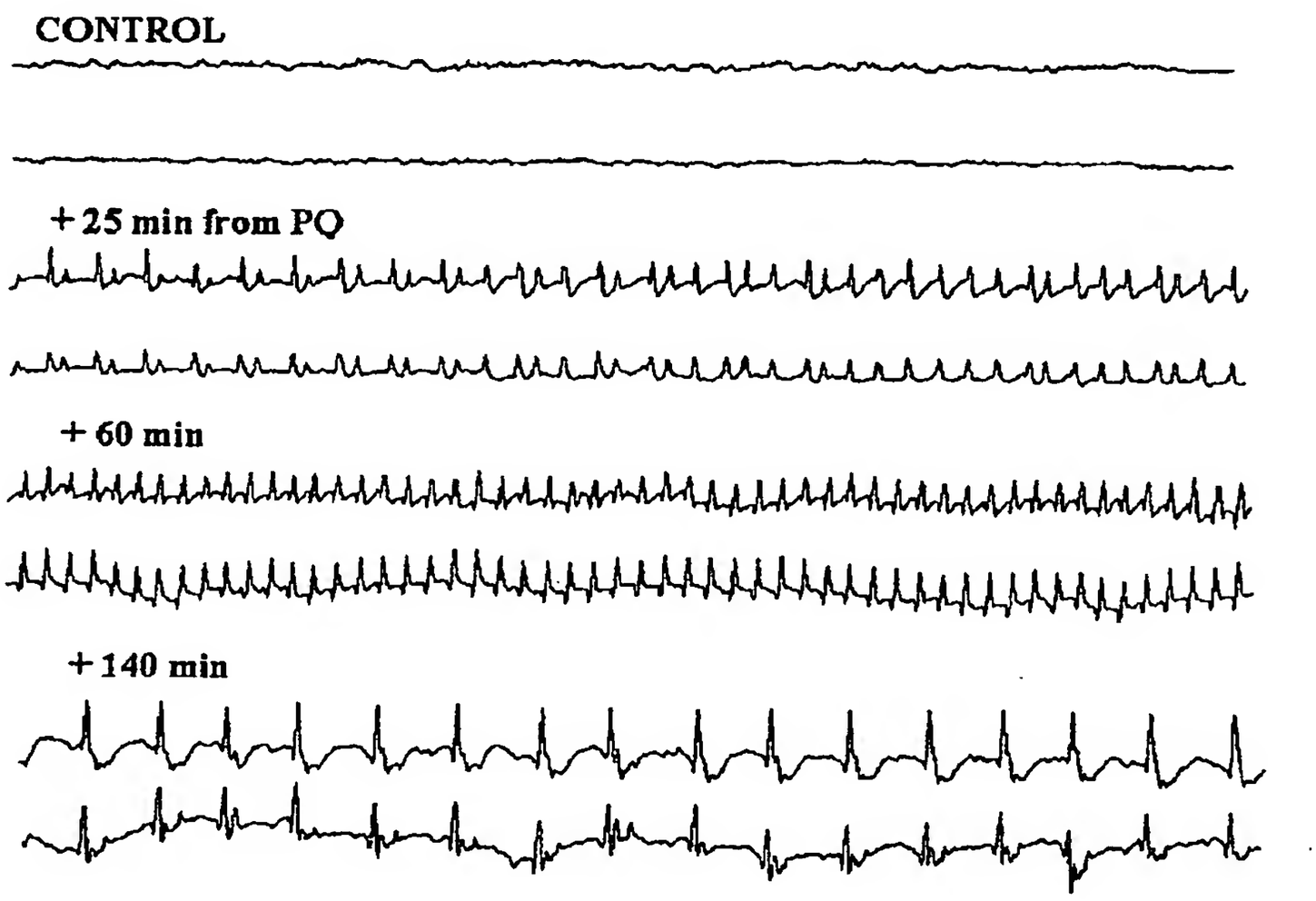
(54) Title: METHOD OF TREATMENT OF NEURODEGENERATIVE DISORDERS



(57) Abstract: The present invention relates to pharmaceutical compositions and methods using such compositions for the treatment of neurodegenerative disorders. Such compositions contain a catalyst for the dismutation of superoxide, including superoxide dismutase enzyme (SOD) and low molecular weight organic ligand derived metal complexes that function as mimics of the enzyme (SOD mimetics or SODms).

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METHOD OF TREATMENT OF NEURODEGENERATIVE DISORDERS

Field of Invention

This invention relates to methods of treatment and inhibition of neurodegenerative disorders in a mammal by administering therapeutic amounts of catalysts for the dismutation of superoxide to the mammal. Also provided are pharmaceutical compositions comprising catalysts for the dismutation of superoxide for use in these methods.

Background of the Invention

Neurodegenerative diseases include Parkinson's disease, Huntington's disease, Alzheimer's disease, and multiple sclerosis. Most of the diseases are typified by onset during the middle adult years and lead to rapid degeneration of specific subsets of neurons within the neural system, ultimately resulting in premature death. There is no known cure for any of the stated diseases.

Parkinson's disease (paralysis agitans) is a common neurodegenerative disorder which appears in mid to late life. Familial and sporadic cases occur, although familial cases account for only 1-2 percent of the observed cases. The neurological changes which cause this disease are somewhat variable and not fully understood. Patients frequently have nerve cell loss with reactive gliosis and Lewy bodies in the substantia nigra and locus coeruleus of the brain stem. Similar changes are observed in the nucleus basalis of Meynert. As a class, the nigrostriatal dopaminergic neurons seem to be most affected.

Parkinson's Disease is a degenerative disease of the nervous system which affects one person in fifty over fifty years of age and one person in twenty over seventy years of age, without gender or social bias. Described by James Parkinson in 1817,the shaking palsy is comprised of a triad of tremor at rest, muscular rigidity and slowness of movement. Accurate description of the disease during the period of the Industrial Revolution has prompted people to speculate that environmental exposure to toxic chemicals precipitates the disease. Exposure to manganese precipitated a Parkinsonian syndrome in miners which also includes schizophreniform behaviors. Some epidemiologic studies have found association between industrial exposure to copper, manganese and copper simultaneously with iron and the incidence of Parkinson's disease, Gorell J. M et al, *Neruoepidemiology*, 18(6), 303-308 (1999), between incidence of Parkinson's disease and blood mercury levels, Ngim C. H. et al, *Neuroepidemiology*, 8(3), 128-141 (1989), and with death rates from Parkinson's Disease and proximity to iron and copper related industrial processes, Rybicki B. A. et al, *Mov. Disord.*, 8(1), 87-92 (1993). Additionally, recent epidemiologic studies indicate that exposure to herbicides and pesticides increase

risk of Parkinson's disease. Gorell, J.M. et al, *Neurology*, 50(5), 1346-50 (May 1998). Xenobiotics, natural and man made insecticides have also been suggested as candidate agents because they precipitate on occasion motor disturbances in animals and man somewhat akin to Parkinsonism. Thus both inorganic and organic chemicals may contribute to the toxicity mechanism. The disease is progressive though not in all cases. Dementia with Alzheimer type pathological changes follows but does not precede the development of Parkinson's Disease in about one quarter of diagnosed cases.

Parkinson's Disease progresses to differing extents in different patients, most commonly over a seven to ten year timeframe from the time of diagnosis. Some patients experience generalized wasting and anorexia, depression and mental changes frequently occur. Approximately one quarter develop Alzheimer type clinical changes in cognitive functioning and measurable Alzheimer pathological changes occur in up to forty percent of cases.

One documented change in the brain of Parkinson's disease patients as well as Alzheimer's disease patients is gliosis, which retards neuronal growth in the brain. Renkawek et al., *"Dementia, Gliosis and Expression of the Small Heat Shock Proteins hsp27 and alpha B-crystallin in Parkinson's Disease"* Neuroreport 1999 Aug 2; 10(11):2273-6. Gliosis is a process in which astrocytes form glial scars in the central nervous system. Since minimizing gliosis can both facilitate neuronal regeneration, there is a need for treatments which inhibit gliosis.

Parkinson's disease generally develops asymmetrically with tremors in one hand o: leg and progresses into symmetrical loss of voluntary movement. Eventually, the patient becomes incapacitated by rigidity and tremors. In the advanced stages the disease is frequently accompanied by dementia.

Diagnosis of Parkinson's disease can only be made after the onset of the disease. Anticholinergic compounds, propranolol, primidone and levodopa are frequently administered to modify neural transmissions and thereby suppress the symptoms of the disease, though there is no known therapy which halts or slows the underlying progression. Deprenyl has shown some therapeutic promise.

Clinical and experimental reports have increased interest in the possibility that environmental chemicals, including herbicides, may be related to the development of Parkinson's disease. *See* Thiruchelvam M. et al, *Brain Res*, 873(2), 225-34 (Aug 11, 2000); Liou H.H. et al, *Neurology*, 48(6), 1583-1588 (Jun 1997). Even though the pathophysiological mechanisms need to be elucidated, it is known that microinfusion of paraquat into *Substantia Nigra* of rats is accompanied by behavioral, electrocortical and neuropathological signs of severe neurotoxicity. *See* Coransanita et al., *Pharmacol. Toxicol.* 83, 1-7 (1998). This effect is however, non-selective and seems to involve an

overproduction of reactive oxygen species (ROS). *See* Iannone et al., *Neuropharmacology,* 30, 893-898 (1991); Murray, R.E., Gibson, J.E., *Toxicol. Appl. Pharmacol.*, 27, 283-291 (1974). The overproduction of reactive oxygen species has also be implicated as contributing, in whole or in part, to other neurodegenerative diseases. *See* Albers et al., *"Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease"* J. Neural Transm Suppl 2000; 59: 133-54. Nevertheless, the use of free-radical scavengers given peripherally has been, so far, unable to produce relevant protective effects in herbicide-related neurodegenerative disorders, an effect which may potentially be due to the difficulty of such compounds in gaining access to the brain in concentrations able to counteract ROS overproduction.

The discovery in the mid 1980's of the neurotoxic effects of the herbicide (MPTP) and MPP^+ on dopaminergic neurons in the Substantia Nigra of the brain led to the hypothesis based on toxin-induced oxidative stress as a potential cause, at least in part, for Parkinson's disease and other neurodegenerative diseases. Foley et al, *"Influence of Neurotoxins and Oxidative Stress on the Onset and Progression of Parkinson's Disease"* J. Neurol 2000 Apr, 247 Suppl 2:II82-94. The herbicides of MPTP and MPP^+ have been used as models for Parkinson's disease. Foley et al, *"Influence of Neurotoxins and Oxidative Stress on the Onset and Progression of Parkinson's Disease"* J. Neurol 2000 Apr, 247 Suppl 2:II82-94. The herbicide called paraquat is structurally similar to MPP+, and both seem to exert their toxic effects by interfering with the first step of electron transport chain of mitochondria, thus blocking respiration and killing the cells. Iannone et al., *"Intra-nigral infusion of Cu-Free Superoxide Dismutase Prevents Paraquat- Induced Behavioural Stimulation and ECoG Epileptogenic Discharges in Rats"* Neuropharm. 30, No. 8 893-898 (1991). The hypothesized mechanisms for the neurotoxic effects of these herbicides further involves an impairment of energy metabolism followed by increased free radical generation. Klivenyi et al., *"Manganese Superoxide Dismutase Overexpression Attenuates MPTP Toxicity"* Neurobiology of Disease 5, 253-258 (1998).

Free radical production, including superoxide anions (O_2^-) and hydroxyl radicals (OH^-) have been implicated as a possible cause of Parkinson's disease as well as other neurodegenerative diseases. Bogdanov et al., *"Increased Oxidative Damage to DNA in ALS Patients"* Free Radic Biol Med 2000 Oct. 1;29(7):652-8; Olanow, C. W., *"An Introduction to the Free Radical Hypothesis in Parkinson's Disease"* Annals of Neurology 32: 52-59 (1992); Albers et al., *"Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease"* J. Neural Transm Suppl 2000; 59: 133-54. One hypothesis is that the free radicals in the brain cause oxidative stress to dopaminergic neurons causing Parkinson-related disorders. Linert et al., *"Redox reactions of neurotransmitters possibly involved in the progression of Parkinson's Disease"* J. Inorg.

Biochem. 79(2000) 319-326. Superoxide anions are normally removed in biological systems by the formation of hydrogen peroxide and oxygen in the following reaction (hereafter referred to as dismutation):

$$0_2^- + 0_2^- + 2H^+ \rightarrow O_2 + H_2O_2$$

This reaction is catalyzed *in vitro* by the ubiquitous superoxide dismutase enzymes.

Recently, a class of non-peptidic, low-molecular weight compounds proven to possess a comparable catalytic activity and the high selectivity of the native superoxide dismutase (SOD) enzymes have been reported and the use of these compounds has been suggested for assessing a better therapeutic approach in diseases mediated by superoxide overproduction (Salvemini et al., *Science* 8, 304-306 (1999)). Several non-peptidic catalysts which mimic this superoxide dismutating activity have been discovered. A particularly effective family of non-peptidic catalysts for the dismutation of superoxide consists of the manganese(II), manganese(III), iron(II) or iron(III) complexes of nitrogen-containing fifteen-membered macrocyclic ligands which catalyze the conversion of superoxide into oxygen and hydrogen peroxide, as described in U.S. Patents Nos. 5,874,421 and 5,637,578, all of which are incorporated herein by reference. *See also*, Weiss, R.H., et al., "Manganese(II)-Based Superoxide Dismutase Mimetics: Rational Drug Design of Artificial Enzymes", *Drugs of the Future* 21: 383-389 (1996); and Riley, D.P., et al., "Rational Design of Synthetic Enzymes and Their Potential Utility as Human Pharmaceuticals" (1997) in CatTech, I, 41. These mimics of superoxide dismutase have been shown to have a variety of therapeutic effects, including anti-inflammatory activity. *See* Weiss, R.H., et al., "Therapeutic Aspects of Manganese (II)-Based Superoxide Dismutase Mimics" In "Inorganic Chemistry in Medicine", (Farrell, N., Ed.), Royal Society of Chemistry, in Press; Weiss, R.H., et al., "Manganese-Based Superoxide Dismutase Mimics: Design, Discovery and Pharmacologic Efficacies" (1995), In "The Oxygen Paradox" (Davies, K.J.A., and Ursini, F., Eds.) pp. 641-651, CLEUP University Press, Padova, Italy; Weiss, R.H., et al., *J. Biol. Chem.*, 271: 26149 (1996); and Hardy, M.M., et al., *J. Biol. Chem.* 269: 18535-18540 (1994). Other non-peptidic catalysts which have been shown to have superoxide dismutating activity are the salen-transition metal cation complexes, as described in U.S. Patent No. 5,696,109 and complexes of porphyrins with iron and manganese cations.

The use of free-radical scavengers, including SOD's and SOD mimics, given peripherally have been unable to produce relevant protective effects in herbicide-related neurodegenerative disorders. Applicants hypothesize that this may be due to the difficulty of such compounds in gaining access to the brain in concentrations able to counteract ROS

overproduction due to the size of the molecules and resulting inability to cross the blood-brain barrier. One of the most notable cellular barriers which drug delivery formulations attempt to circumvent is the blood-brain barrier (BBB), which is composed of 95% brain capillary endothelium. Clinical observations indicate that drug delivery across the BBB is a major factor in the management of the many central nervous system (CNS) diseases, such as primary or metastatic tumors in the brain, primary or secondary CNS infection in AIDS, neurological degenerations in Parkinson's disease, multiple sclerosis, and genetic enzyme deficiencies. *See* U.S. Patent No. 5,254,342.

The blood-brain barrier, which consists of the endothelium of the brain vessels, the basal membrane and neuroglial cells, acts to limit penetration of substances into the brain. Sometimes the structure of the BBB is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier Banks, W. A., Kastin, A. J., Barrera, "Delivering peptides to the central nervous system: Dilemmas and strategies," Pharm. Res. 8:1345-1350(1991). The nature of the substance penetration through the BBB has not yet been determined but it is known that many of the regulators of brain function such as cytokines, transferrin, encephalins and endorphines can pass through the bbb from the blood vessels into the brain. Raeissi, S., Audus, J., "In vitro characterization of blood-brain barrier permeability to delta sleep-inducing peptide." J. Pharm. Phy. 41:848-852(1989); Zlokovich, B., Susie, V. T., Davson, H. Begley, D. J., Jankov, R. M., Mitrivic, B. M., Lipovac, M. N., "Saturable mechanism for delta sleep-inducing peptide (DSIP) at the blood-brain barrier of the vascularly perfused guinea pig brain." Peptides 10:249-254(1989); and Zlokovich, B., "In vivo approaches for studying peptide interaction at the blood-brain barrier." J. Control. Rel. 13:185-201(1990). However, many substances which can affect the Central Nervous System (or CNS) and brain such as macromolecules penetrate poorly or not at all through the BBB. At present, drugs with no BBB penetration or poor BBB penetration can only be given by direct CNS infusion or by implantation of controlled-release polymers. (See, e.g., U.S. Pat. No. 4,883,666, Sabel et al.) Thus, many potentially potent drugs are not useful clinically due to their inability to pass the BBB. Macromolecules, such as proteins, do not pass the BBB at all due to the size of the molecule. Since size is one of the factors in allowing permeability of the BBB, some researchers attempt to isolate only the active portion of the macromolecule for administration. The reduced size of the resulting product is used in the hope that the smaller molecule can now pass the BBB. *See* U.S. Patent No. 6,117,454.

Thus, the need presently exists for compositions able to cross the blood-brain barrier and methods for preventing and treating Parkinson's Disease and other neurodegenerative disorders associated with the overproduction of ROS in these subjects.

Summary of the Invention

Accordingly, an object of the present invention is to provide a method of treating neurodegenerative disorders, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a non-proteinaceous catalyst for the dismutation of superoxide anions.

Another object of the present invention is to provide a pharmaceutical composition for the treatment of neurodegenerative disorders comprising a non-proteinaceous catalyst for the dismutation of superoxide anions and a pharamaceutically acceptable carrier.

A further object of the present invention is to provide a method for treatment of oxidative stress to the components of neurons, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a non-proteinaceous catalyst for the dismutation of superoxide anions.

Yet another object of the present invention is to provide a method for treatment of gliosis, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a catalyst for the dismutation of superoxide anions.

Other objects and features will be in part apparent and in part pointed out hereinafter.

Brief Description of the Figures

Figure 1(a) is a graph of high voltage epileptogenic discharges induced at various times (at 25 minutes, at 60 minutes and at 140 minutes) after infusion of paraquat into the substantia nigra of rats.

Figure 1(b) is a graph of high voltage epileptogenic discharges induced after administration of 10 μg of the SOD mimic M40401 given in the substantia Nigra of rats with administration, 15 minutes later, of paraquat in the subtantia nigra of these rats. The measurements were taken at various times after the administration of the paraquat (at 30 minutes, 60 minutes and 140 minutes).

Figure 2(a) is a histopathologic image of the neuropathological effects of a single unilateral injection of Paraquat (50 μg) into the Substantia Nigra of a vehicle-treated rat.

Figure 2(b) is a histopathologic image of the neuropathological effects on the Substantia Nigra from a rat pretreated with 1 μl of saline, and 15 minutes later, given 50 μg of Paraquat.

Figure 2(c) is a histopathologic image of the neuropathologic effects on the Substantia Nigra from a rat pretreated with 10 μg of M40401, and 15 minutes later, given 50 μg of Paraquat. A marked neuroprotection is evident from the image.

Abbreviations and Definitions

As used herein, the terms "reactive oxygen species" or "ROS" refers to a toxic superoxide anion (O_2^-). The superoxide anion, as well as the nitric oxide (NO^-) and the hydroxyl radical (OH^-)are different types of free-radicals.

As used herein, the terms "non-peptidic catalysts for the dismutation of superoxide" or "non-proteinaceous catalysts for the dismutation of superoxide" mean a low-molecular weight catalyst for the conversion of superoxide anions into hydrogen peroxide and molecular oxygen. These catalysts commonly consist of an organic ligand and a chelated transition metal ion, preferably manganese(II), manganese(III), iron(II) or iron(III). The term may include catalysts containing short-chain polypeptides (under 15 amino acids) or macrocyclic structures derived from amino acids, as the organic ligand. The term explicitly excludes a superoxide dismutase enzyme obtained from any species.

The term "substituted" means that the described moiety has one or more substituents comprising at least 1 carbon or heteroatom, and further comprising 0 to 22 carbon atoms, more preferably from 1 to 15 carbon atoms, and comprising 0 to 22 heteroatoms, more preferably from 0 to 15 heteroatoms. As used herein, "heteroatom" refers to those atoms that are neither carbon nor hydrogen bound to carbon and are selected from the group consisting of: O, S, N, P, Si, B, F, Cl, Br, or I. These atoms may be arranged in a number of configurations, creating substituent groups which are unsaturated, saturated, or aromatic. Examples of such substituents include branched or unbranched alkyl, alkenyl, or alkynyl, cyclic, heterocyclic, aryl, heteroaryl, allyl, polycycloalkyl, polycycloaryl, polycycloheteroaryl, imines, aminoalkyl, hydroxyalkyl, hydroxyl, phenol, amine oxides, thioalkyl, carboalkoxyalkyl, carboxylic acids and their derivatives, keto, ether, aldehyde, amine, amide, nitrile, halo, thiol, sulfoxide, sulfone, sulfonic acid, sulfide, disulfide, phosphonic acid, phosphinic acid, acrylic acid, sulphonamides, amino acids, peptides, proteins, carbohydrates, nucleic acids, fatty acids, lipids, nitro, hydroxylamines, hydroxamic acids, thiocarbonyls, thiocarbonyls, borates, boranes, boraza, silyl, silaza, siloxy, and combinations thereof.

The term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 22 carbon atoms, preferably from about 1 to about 18 carbon atoms, and most preferably from about 1 to about 12 carbon atoms. Examples of such radicals include, but are not limited to, methyl, ethyl, n-propyl,

isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, octadecyl and eicosyl.

The term "alkenyl", alone or in combination, means an alkyl radical having one or more double bonds. Examples of such alkenyl radicals include, but are not limited to, ethenyl, propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl, iso-butylenyl, cis-2-pentenyl, trans-2-pentenyl, 3-methyl-1-butenyl, 2,3-dimethyl-2-butenyl, 1-pentenyl, 1-hexenyl, 1-octenyl, decenyl, dodecenyl, tetradecenyl, hexadecenyl, cis- and trans-9-octadecenyl, 1,3-pentadienyl, 2,4-pentadienyl, 2,3-pentadienyl, 1,3-hexadienyl, 2,4-hexadienyl, 5,8,11,14-eicosatetraenyl, and 9,12,15-octadecatrienyl.

The term "alkynyl", alone or in combination, means an alkyl radical having one or more triple bonds. Examples of such alkynyl groups include, but are not limited to, ethynyl, propynyl (propargyl), 1-butynyl, 1-octynyl, 9-octadecynyl, 1,3-pentadiynyl, 2,4-pentadiynyl, 1,3-hexadiynyl, and 2,4-hexadiynyl.

The term "cycloalkyl", alone or in combination means a cycloalkyl radical containing from 3 to about 10, preferably from 3 to about 8, and most preferably from 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and perhydronaphthyl.

The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of cycloalkylalkyl radicals include, but are not limited to, cyclohexylmethyl, cyclopentylmethyl, (4-isopropylcyclohexyl)methyl, (4-t-butyl-cyclohexyl)methyl, 3-cyclohexylpropyl, 2-cyclohexylmethylpentyl,3-cyclopentylmethylhexyl, 1-(4-neopentylcyclohexyl)methylhexyl, and 1-(4-isopropylcyclohexyl)methylheptyl.

The term "cycloalkylcycloalkyl" means a cycloalkyl radical as defined above which is substituted by another cycloalkyl radical as defined above. Examples of cycloalkylcycloalkyl radicals include, but are not limited to, cyclohexylcyclopentyl and cyclohexylcyclohexyl.

The term "cycloalkenyl", alone or in combination, means a cycloalkyl radical having one or more double bonds. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl and cyclooctadienyl.

The term "cycloalkenylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkenyl radical as defined above. Examples of cycloalkenylalkyl radicals include, but are not limited to, 2-cyclohexen-1-ylmethyl,

1-cyclopenten-1-ylmethyl, 2-(1-cyclohexen-1-yl)ethyl, 3-(1-cyclopenten-1-yl)propyl, 1-(1-cyclohe: 1-(1-cyclopenten-1-yl)hexyl, 6-(1-cyclohexen-1-yl)hexyl, 1-(1-cyclopenten-1-yl)nonyl and 1-(1-cyclohexen-1-yl)nonyl.

The terms "alkylcycloalkyl" and "alkenylcycloalkyl" mean a cycloalkyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkyl and alkenylcycloalkyl radicals include, but are not limited to, 2-ethylcyclobutyl, 1-methylcyclopentyl, 1-hexylcyclopentyl, 1-methylcyclohexyl, 1-(9-octadecenyl)cyclopentyl and 1-(9-octadecenyl)cyclohexyl.

The terms "alkylcycloalkenyl" and "alkenylcycloalkenyl" means a cycloalkenyl radical as defined above which is substituted by an alkyl or alkenyl radical as defined above. Examples of alkylcycloalkenyl and alkenylcycloalkenyl radicals include, but are not limited to, 1-methyl-2-cyclopentyl, 1-hexyl-2-cyclopentenyl, 1-ethyl-2-cyclohexenyl, 1-butyl-2-cyclohexenyl, 1-(9-octadecenyl)-2-cyclohexenyl and 1-(2-pentenyl)-2-cyclohexenyl.

The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, cycloalkyl, cycloalkenyl, aryl, heterocycle, alkoxyaryl, alkaryl, alkoxy, halogen, hydroxy, amine, cyano, nitro, alkylthio, phenoxy, ether, trifluoromethyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like.

The term "aralkyl", alone or in combination, means an alkyl or cycloalkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl, and the like.

The term "heterocyclic" means ring structures containing at least one heteroatom within the ring. As used herein, "heteroatom" refer to atoms that are neither carbon nor hydrogen bound to a carbon. Examples of heterocyclics include, but are not limited to, pyrrolidinyl, piperidyl, imidazolidinyl, tetrahydrofuryl, tetrahydrothienyl, furyl, thienyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, benzoxadiazolyl, benzothiadiazolyl, triazolyl and tetrazolyl groups.

The term "saturated, partially saturated or unsaturated cyclic" means fused ring structures in which 2 carbons of the ring are also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 3 to 20 carbon atoms, preferably 5 to 10 carbon atoms, and can also contain one or more other kinds of atoms in addition to carbon. The most common of the other kinds of atoms include nitrogen, oxygen and sulfur. The ring structure can also contain more than one ring.

The term "saturated, partially saturated or unsaturated ring structure" means a ring structure in which one carbon of the ring is also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 3 to 20, preferably 5 to 10, carbon atoms and can also contain nitrogen, oxygen and/or sulfur atoms.

The term "nitrogen containing heterocycle" means ring structures in which 2 carbons and a nitrogen of the ring are also part of the fifteen-membered macrocyclic ligand. The ring structure can contain 2 to 20, preferably 4 to 10, carbon atoms, can be substituted or unsubstituted, partially or fully unsaturated or saturated, and can also contain nitrogen, oxygen and/or sulfur atoms in the portion of the ring which is not also part of the fifteen-membered macrocyclic ligand.

The term "organic acid anion" refers to carboxylic acid anions having from about 1 to about 18 carbon atoms.

The term "halide" means chloride, fluoride, iodide, or bromide.

As used herein, "R" groups means all of the R groups attached to the carbon atoms of the macrocycle, *i.e.*, R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, R'_9.

The mammal patient in the methods of the invention is a mammal suffering from Parkinson's disease or other neurodegenerative disorder. It is envisioned that a mammal patient to which the catalyst for the dismutation of superoxide will be administered, in the methods or compositions of the invention, will be a human. However, other mammal patients in veterinary (*e.g.*, companion pets and large veterinary animals) and other conceivable contexts are also contemplated.

As used herein, the terms "treatment" or "treating" relate to any treatment of Parkinson's disease and other neurodegenerative disorders and include: (1) preventing Parkinson's disease or other neurodegenerative disorder from occurring in a subject; (2) inhibiting the progression or initiation of neurodegeneration, *i.e.*, arresting or limiting its development; or (3) ameliorating or relieving the symptoms of the disease.

As used herein, the term "neurodegenerative disorder" relates to any disease, such as Parkinson's disease, Huntington's disease, multiple sclerosis, and Alzheimer disease, or any other disorder relating to or marked by nervous degeneration related to reactive oxygen species.

The term "precursor ligand" means the organic ligand of a SOD mimic without the chelated transition metal cation and charge neutralizing anions.

The term "therapeutically effective amounts" means those amounts that, when administered to a particular subject in view of the nature and severity of that subject's disease or condition, will have the desired therapeutic effect, e.g., an amount which will cure, or at least partially arrest or inhibit the disease or condition.

All references cited herein are explicitly incorporated by reference.

Detailed Description of the Invention

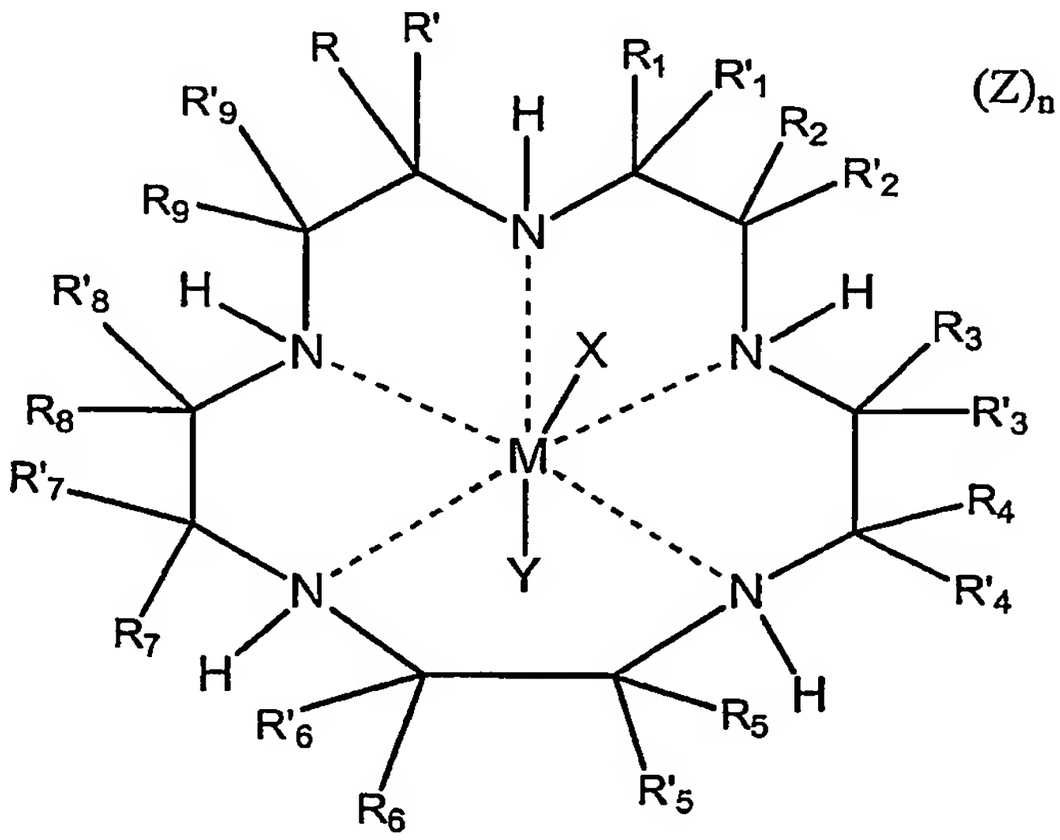
The present invention is directed to methods and compositions for the prevention and treatment of Parkinson's disease and other neurodegenerative disorders comprising administering compositions containing a non-proteinaceous catalyst for dismutation of superoxide. Preferred catalysts include a small molecular weight organic ligand mimics of the superoxide dismutase enzyme (SOD mimetics or SODms).

A basis for the present invention is the finding that treatment with a catalyst for the dismutation of superoxide inhibits the progression and initiation of neurodegenerative diseases. It is believed that such neurodegenerative diseases result, in whole or in part, from oxidative stress mediated by overproduction of superoxide anions. *See* Bogdanov et al., *"Increased Oxidative Damage to DNA in ALS Patients"* Free Radic Biol Med 2000 Oct. 1;29(7):652-8; Olanow, C. W., "*An Introduction to the Free Radical Hypothesis in Parkinson's Disease*" Annals of Neurology 32: 52-59 (1992); Albers et al., *"Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease"* J. Neural Transm Suppl 2000; 59: 133-54. Applicant's believe, without being bound by a particular theory or mechanism, that the SOD's of this invention remove O_2^- from brain tissue, thereby protecting brain tissue from damage to the essential components of the dopaminergic neurons, and from lipid peroxidation. As a result, neurodegeneration is reversed and symptoms of the disease are improved. It is hypothesized that the oxygen free radicals react with essential components of dopaminergic neurons resulting in functional disruption and ultimately cell death. *See* Foley, et al., *"Influence of Neurotoxis and Oxidative Stress on the Onset and Progression of Parkinson's Disease"*, J.Neurol 2000 Apr;247 Suppl2:II82-94. Also, it is hypothesized that the ROS react with the membrane phospholipids in the brain leading to lipid peroxidation and irreversible brain cell death. *See* Foley, et al., *"Influence of Neurotoxis and Oxidative Stress on the Onset and Progression of Parkinson's Disease"*, J.Neurol 2000 Apr;247 Suppl2:II82-94.

Preferably, the compound employed in the method of the present invention will comprise a non-proteinaceous catalyst for the dismutation of superoxide anions ("SOD mimic") as opposed to a native form of the SOD enzyme. As utilized herein, the term "SOD mimic" means a low-molecular-weight catalyst for the conversion of superoxide anions into hydrogen peroxide and molecular oxygen. These catalysts consist of an organic ligand having a pentaazacyclopentadecane portion and a chelated transition metal ion, preferably manganese or iron. The term may include catalysts containing short-chain polypeptides (under 15 amino acids), or macrocyclic structures derived from amino acids, as the organic ligand. The term explicitly excludes a SOD enzyme obtained from any

natural sources. SOD mimics are useful in the method of the present invention as compared to native SOD because of the limitations associated with native SOD therapies such as, solution instability, limited cellular accessibility due to their size, immunogenicity, bell-shaped dose response curves, short half-lives, costs of production, and proteolytic digestion (Salvemini et al., (1999) Science 286: 304-306). For example, the best known native SOD, CuZn, has a molecular weight of 33,000 kD. Contrastingly, SOD mimics have an approximate molecular weight of 500 to 600 kD. The compounds employed in the method of the invention must be able to efficiently cross the blood brain barrier to penetrate the cerebral cavity in order to cause the dismutation of superoxide anions. Therefore, the smaller size exhibited by the SOD mimics is particularly advantageous for the present invention because it facilitates passage of the compound through the blood brain barrier and into the cerebral cavity.

In a particularly preferred embodiment, the SOD mimics utilized in the present invention comprise an organic ligand chelated to a metal ion. Particularly preferred catalysts are pentaaza-macrocyclic ligand compounds, more specifically the manganese(II), manganese (III), iron(II) and iron(III) chelates of pentaazacyclopentadecane compounds. The pentaaza macrocyclic ligand complexes of Mn(II) are particularly advantageous for use in the present invention because, in addition to a low molecular weight, they are highly selective for the dismutation of super oxide anions and possess catalytic rates similar or faster than native SOD counterparts. An example of this class of SOD mimic, M40401, is set forth in the examples below. These pentaazacyclopentadecane compounds can be represented by the following formula:

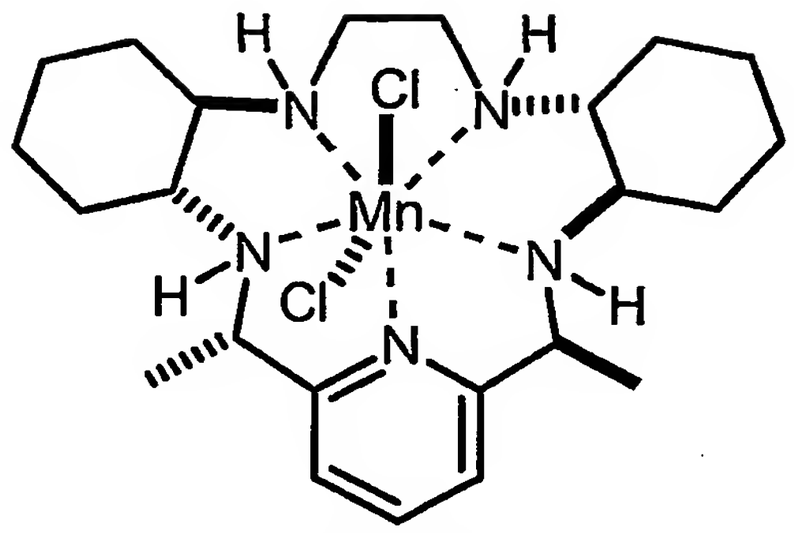


wherein M is a cation of a transition metal, preferably manganese or iron; wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a substituted or unsubstituted, saturated, partially saturated or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; R or R' and R_1 or R'_1, R_2 or R'_2 and R_3 or R'_2, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, and R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the included carbon atoms of the macrocycle are absent; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9 and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula:

$$-(CH2)_x-M-(CH2)_w-L-(CH2)_z-I-(CH2)_y-$$

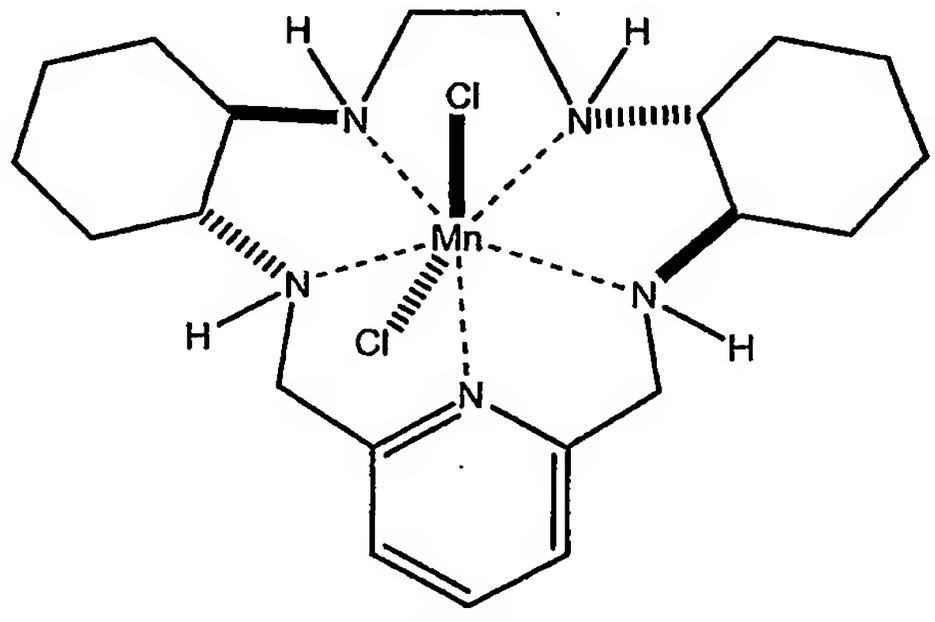
wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof.

A preferred compound of this class of pentaaza-macrocyclic class is designated M40401 and is represented by the following formula:



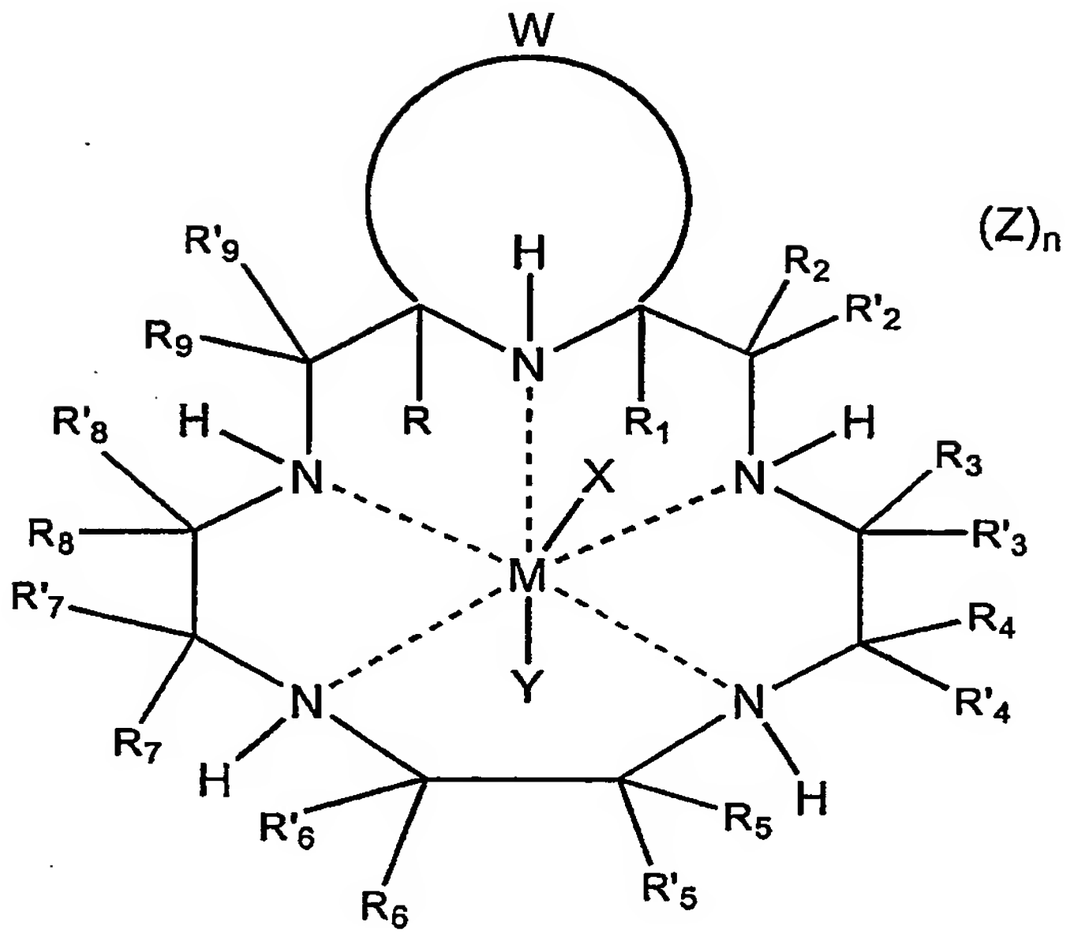
M40401

Another perferred compound of this class of pentaaza-macrocyclic class is designated M40403 and is represented by the following formula:



M40403

In another embodiment, the catalysts are substituted pentaaza-macrocyclic ligand compounds, which may be represented by the following formula:



wherein a nitrogen of the macrocycle and the two adjacent carbon atoms to which it is attached independently form a substituted, unsaturated, nitrogen-containing heterocycle W having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;

and wherein R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; and, optionally, one or more of R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, or R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and, optionally, one or more of R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and, optionally, one of R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R_1,, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6,

R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations of any of the above; wherein M is a cation of a transition metal selected from the group consisting of manganese and iron; and wherein X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof.

In a particularly preferred embodiment, the substituted pentaaza-macrocyclic ligand set forth above, W is a substituted pyridino moiety and U and V are trans-cyclohexanyl fused rings. In addition, the pentaaza-macrocyclic or substituted pentaaza-macrocyclic ligand compounds useful in the present invention can have any combinations of substituted or unsubstituted R groups, saturated, partially saturated or unsaturated cyclics, ring structures, nitrogen containing heterocycles, or straps as defined above.

X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). X, Y and Z are independently selected from the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), àryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl

phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins. The preferred ligands from which X, Y and Z are selected include halide, organic acid, nitrate and bicarbonate anions.

The "R" groups attached to the carbon atoms of the macrocycle can be in the axial or equatorial position relative to the macrocycle. When the "R" group is other than hydrogen or when two adjacent "R" groups, *i.e.*, on adjacent carbon atoms, together with the carbon atoms to which they are attached form a saturated, partially saturated or unsaturated cyclic or a nitrogen containing heterocycle, or when two R groups on the same carbon atom together with the carbon atom to which they are attached form a saturated, partially saturated or unsaturated ring structure, it is preferred that at least some of the "R" groups are in the equatorial position for reasons of improved activity and stability. This is particularly true when the complex contains more than one "R" group which is not hydrogen.

A wide variety of pentaaza-macrocyclic ligand compounds with superoxide dismutating activity may be readily synthesized. Generally, the transition metal center of the catalyst is thought to be the active site of catalysis, wherein the manganese or iron ion cycles between the (II) and (III) states. Thus, as long as the redox potential of the ion is in a range in which superoxide anion can reduce the oxidized metal and protonated superoxide can oxidize the reduced metal, and steric hindrance of the approach of the superoxide anion is minimal, the catalyst will function with a k_{cat} of about 10^{-6} to 10^{-8}.

The pentaaza-macrocyclic ligand compound catalysts described have been further described in U.S. Patent No. 5,637,578, PCT application WO98/58636, and copending application USSN 09/398,120, all of which are hereby incorporated by reference. These pentaaza-macrocyclic ligand catalysts may be produced by the methods disclosed in U.S. Patent No. 5,610,293. However, it is preferred that the pentaaza-macrocyclic ligand compound catalysts used in the present invention be synthesized by the template method

described in copending applications USSN 60/136,298 and USSN 09/398,120, incorporated herein by reference.

Activity of the compounds or complexes of the present invention for catalyzing the dismutation of superoxide can be demonstrated using the stopped-flow kinetic analysis technique as described in Riley, D.P. et al., *Anal. Biochem.*, 196: 344-349 (1991) which is incorporated herein by reference. Stopped-flow kinetic analysis is an accurate and direct method for quantitatively monitoring the decay rates of superoxide in water. The stopped-flow kinetic analysis is suitable for screening compounds for SOD activity and activity of the compounds or complexes of the present invention, as shown by stopped-flow analysis, correlate to treating the above disease states and disorders.

Contemplated equivalents of the general formulas set forth above for the compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties such as tautomers of the compounds and such as wherein one or more of the various R groups are simple variations of the substituents as defined therein, *e.g.*, wherein R is a higher alkyl group than that indicated, or where the tosyl groups are other nitrogen or oxygen protecting groups or wherein the O-tosyl is a halide. Anions having a charge other than 1, *e.g.*, carbonate, phosphate, and hydrogen phosphate, can be used instead of anions having a charge of 1, so long as they do not adversely affect the overall activity of the complex. However, using anions having a charge other than 1 will result in a slight modification of the general formula for the complex set forth above. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, *e.g.*, a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure. Further, it is contemplated that manganese(III) complexes will be equivalent to the subject manganese(II) complexes.

For use in treatment or prophylaxis of subjects, the compounds of the invention can be formulated as pharmaceutical or veterinary compositions. Depending on the subject to be treated, the mode of administration, and the type of treatment desired (*e.g.*, inhibition, prevention, prophylaxis, therapy), the compounds are formulated in ways consonant with these parameters. The compositions of the present invention comprise a therapeutically or prophylactically effective dosage of a catalyst for the dismutation of superoxide. The catalyst for the dismutation of superoxide is preferably a SOD mimetic, as described in more detail above. The SODms of this invention are preferably used in combination with a pharmaceutically acceptable carrier.

The compositions of the present invention may be incorporated in conventional pharmaceutical formulations (*e.g.* injectable solutions) for use in treating humans or

animals in need thereof. Pharmaceutical compositions can be administered by subcutaneous, intravenous, or intramuscular injection, or as large volume parenteral solutions and the like. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

For example, a parenteral therapeutic composition may comprise a sterile isotonic saline solution containing between 0.1 percent and 90 percent weight to volume of the catalysts for the dismutation of superoxide. A preferred solution contains from about 5 percent to about 20 percent, more preferably from about 5 percent to about 17 percent, more preferably from about 8 to about 14 percent, and most preferably about 10 percent catalysts for dismutation of superoxide in solution (% weight per volume).

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be appreciated that the unit content of active ingredients contained in an individual dose of each dosage form need not in itself constitute an effective amount, as the necessary effective amount could be reached by administration of a number of individual doses. The selection of dosage depends upon the dosage form utilized, the condition being treated, and the particular purpose to be achieved according to the determination of those skilled in the art.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The pharmaceutical compositions of the present invention are preferably administered to a human. However, besides being useful for human treatment, these extracts are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, cats, sheep, and pigs.

The detailed description set-forth above is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variation in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

All publications, patents, patent applications and other references cited in this application are herein incorporated by reference in their entirety as if each individual publication, patent, patent application or other reference were specifically and individually indicated to be incorporated by reference.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Example 1

In this experiment we demonstrate that both intracerebral and peripheral administration of M40401, a non-peptidic SOD mimic of the type described herein, protected against paraquat-induced behavioral, electrocortical (EcoG) and neuropathological effects in rats. In particular, microinfusion of paraquat into the *Substantia Nigra* produced increased motor activity, jumping and circling opposite to the injection site, associated with ECoG desynchronisation, high voltage epileptogenic spikes and with neuropathological changes characterised by nuclear pyknosis, chromatolisis, gliosis and neuronal cell loss in the injection site (Fig. 1a and 2b). All the animals died 24 hrs after the microinfusion. Pre-treatment of rats with 1-10 μg of M40401 given directly into the *Substantia Nigra* (n=5) significantly prolonged the latency of onset of the intensity of electrocortical and behavioral effects induced by the subsequent injection of paraquat (50 μg; 15 min later) (data with the 10 μg dose is shown in Fig. 1b and 2c). In addition, in M40401- pretreated rats paraquat produced only slight neuronal damage and moderate gliosis limited to the injection site. Furthermore, the protection by M40401 was seen also after peripheral administration of this SOD mimic. Motor convulsion, ECoG epileptogenic discharge and neurodegenerative effects observed with intranigral injection of paraquat (50 μg) were attenuated in a dose dependent fashion by M40401 (1-10 mg/kg i.p.; n=5, not shown). M40401 at 5 and 10 mg/kg completely prevented mortality by 100% (n=5), at 2.5 mg/kg by 70% and at 1 mg/kg by 30% (n=5). Both peripheral and central injection of M40401 significantly reduced malonyldialdehyde formation in brain tissues subsequent to paraquat injection, thus confirming that the SOD mimic compound protected against lipid peroxidation due to the herbicide administration in rats (not shown).

These results demonstrate that restoring antioxidant (SOD) levels in brain tissues by using M40401, a highly active prototype of a class of novel catalytic antioxidants able to cross the blood brain barrier, is crucial in protecting dopaminergic neurons of *Substantia Nigra* against the neurodegenerative insult produced by herbicides such as paraquat. This represents a useful approach in the treatment of many neurodegenerative disorders, including Parkinsons's disease.

What is claimed is:

1. A method of treating neurodegenerative disorders, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a non-proteinaceous catalyst for the dismutation of superoxide anions.

2. The method of claim 1 wherein treatment of neurodegenerative disorders is achieved by inhibiting oxidative stress to the components of neurons.

3. The method of claim 2 wherein the oxidative stress is mediated by superoxide anions.

4. The method of claim 2 wherein the neurons are dopaminergic neurons.

5. The method of claim 1 wherein treatment of neurodegenerative disorders is achieved by limiting neural cell death.

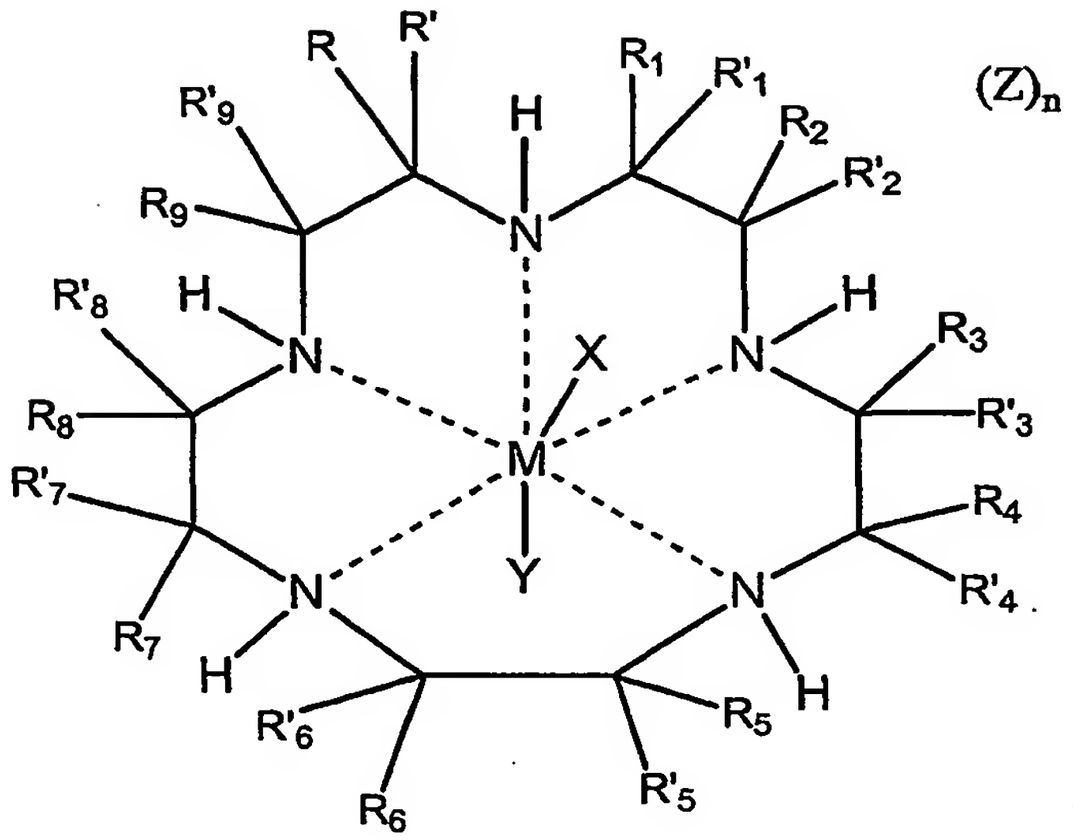
6. The method of claim 5 wherein the neural cell death is limited by preventing oxidative stress mediated by superoxide anions.

7. The method of claim 1 wherein the neurodegenerative disorder is Parkinson's disease.

8. The method of claim 1 wherein the non-proteinaceous catalyst for the dismutation of superoxide anions comprises an organic ligand chelated to a metal ion selected from the group of manganese(II), manganese(III), iron(II) and iron(III).

9. The method of claim 8 wherein the non-proteinaceous catalyst is a pentaaza-macrocyclic ligand complex or a substituted pentaaza-macrocyclic ligand complex.

10. The method of claim 9 wherein the pentaaza-macrocyclic ligand complex is represented by the following formula:



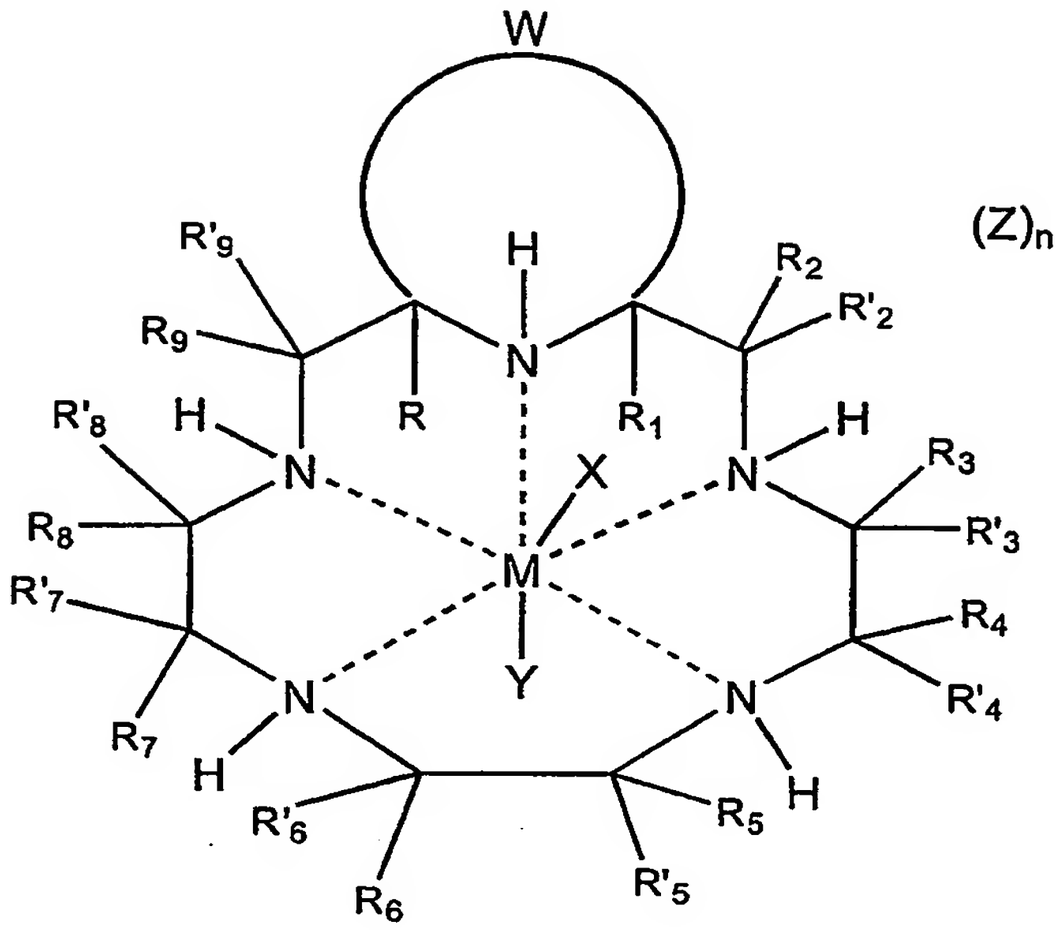
wherein M is a cation of a transition metal, preferably manganese or iron; wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a substituted or unsubstituted, saturated, partially saturated or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; R or R' and R_1 or R'_1, R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, and R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the included carbon atoms of the macrocycle are absent; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations thereof;

and wherein X, Y and Z are independently selected from the group consisting of halide, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), aryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins.

11. The method of claim 9 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:



wherein a nitrogen of the macrocycle and the two adjacent carbon atoms to which it is attached independently form a substituted, unsaturated, nitrogen-containing heterocycle W having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and wherein R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl; cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; and, optionally, one or more of R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, or R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and, optionally, one or more of R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and, optionally, one of R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R_1,, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8,

R'$_8$, R$_9$, and R'$_9$ which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations of any of the above; wherein M is a cation of a transition metal selected from the group consisting of manganese and iron; and wherein X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof.

12. The substituted pentaaza-macrocyclic ligand complex of claim 11 wherein U and V are trans-cyclohexanyl fused rings.

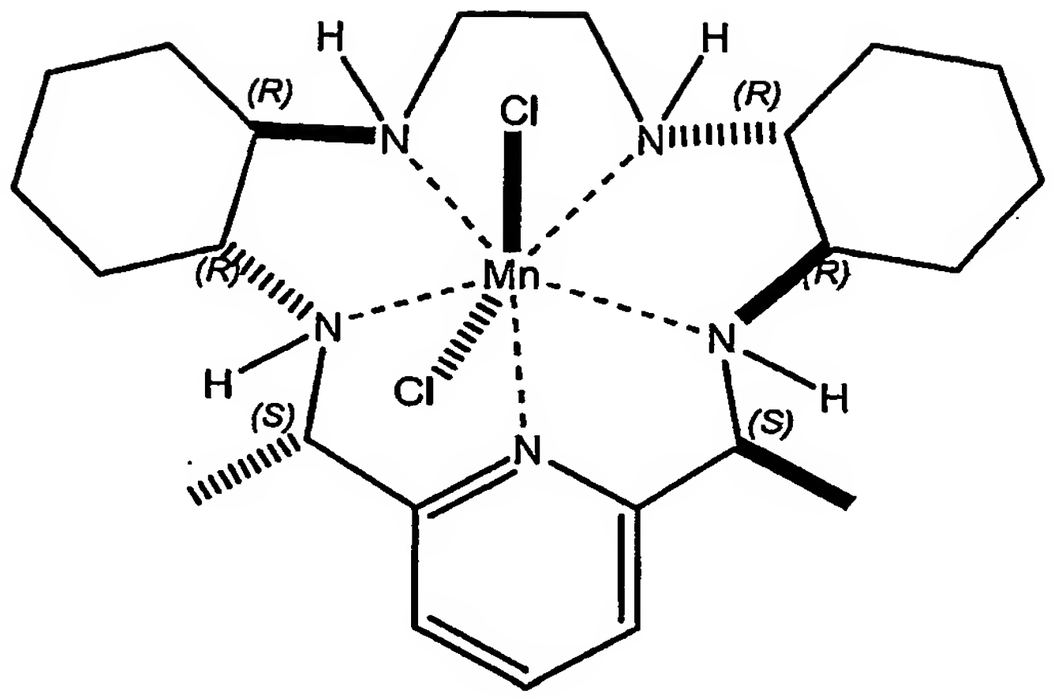
13. The substituted pentaaza-macrocyclic ligand complex of claim 11 wherein W is a substituted pyridino moiety.

14. The substituted pentaaza-macrocyclic ligand complex of claim 11 wherein U and V are trans-cyclohexanyl fused rings and W is a substituted pyridino moiety.

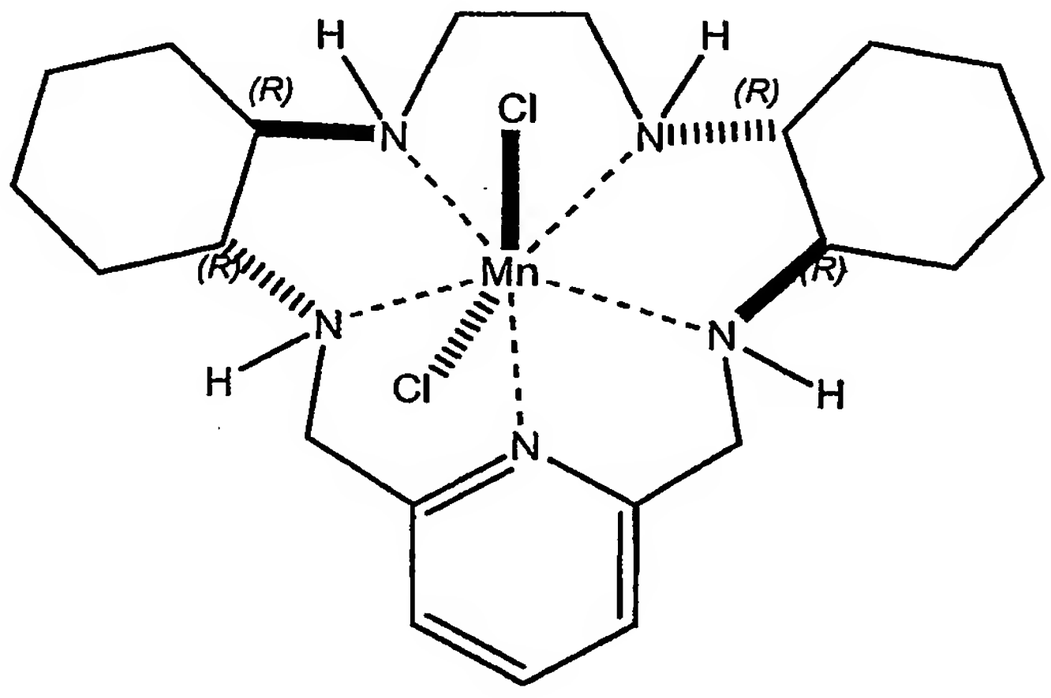
15. The method of claim 1 wherein the subject is a mammal.

16. The method of claim 15 wherein the mammal is a human.

17. A method of claim 9 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:



18. A method of claim 9 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:



19. A pharmaceutical composition for the treatment of neurodegenerative disorders comprising a non-proteinaceous catalyst for the dismutation of superoxide anions and a pharmaceutically acceptable carrier.

20. A method for treatment of oxidative stress to the components of neurons, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a non-proteinaceous catalyst for the dismutation of superoxide anions.

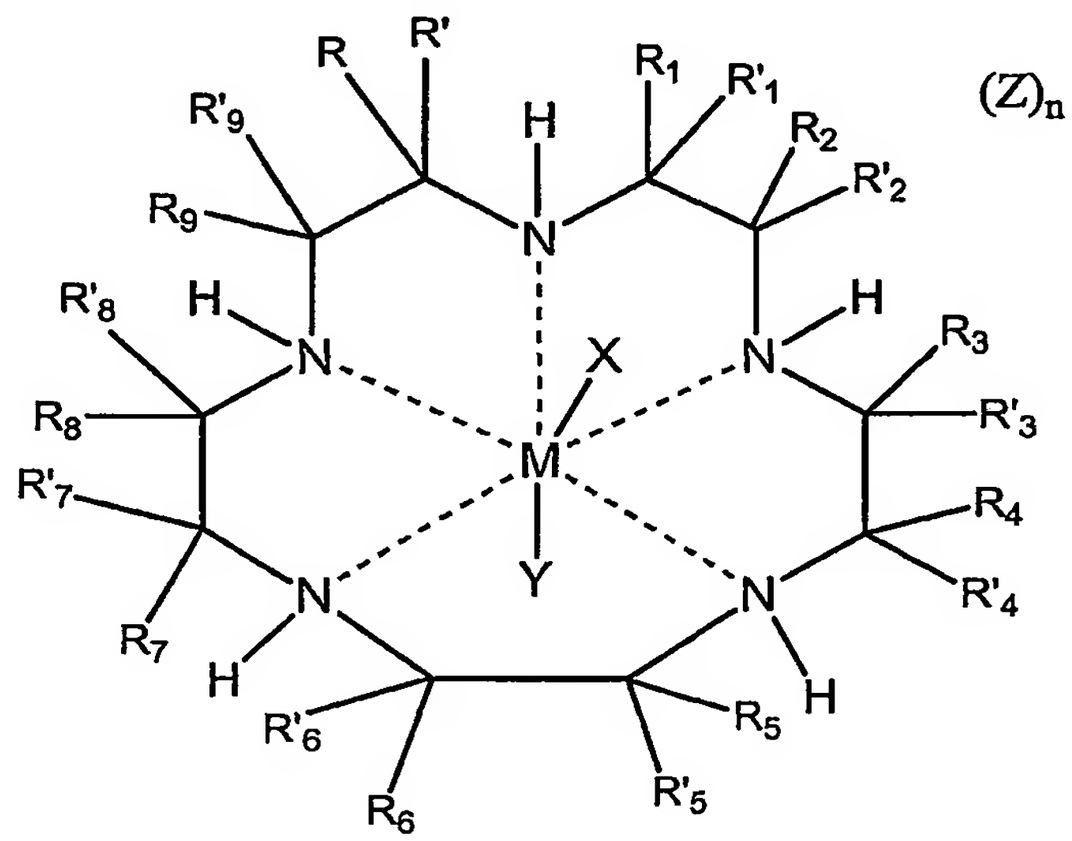
21. A method of claim 20 wherein the oxidative stress is mediated by superoxide anions.

22. The method of claim 20 wherein the neurons are dopaminergic neurons.

23. The method of claim 20 wherein the non-proteinaceous catalyst comprises an organic ligand chelated to a metal ion selected from the group of manganese(II), manganese(III), iron(II) and iron(III).

24. The method of claim 23 wherein the non-proteinaceous catalyst is a pentaaza-macrocyclic ligand complex or a substituted pentaaza-macrocyclic ligand complex.

25. The method of claim 24 wherein the pentaaza-macrocyclic ligand complex is represented by the following formula:



wherein M is a cation of a transition metal, preferably manganese or iron; wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a substituted or unsubstituted, saturated, partially saturated or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; R or R' and R_1 or R'_1, R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, and R_8 or R'_8 and R_9 or R'_9

together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the included carbon atoms of the macrocycle are absent; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

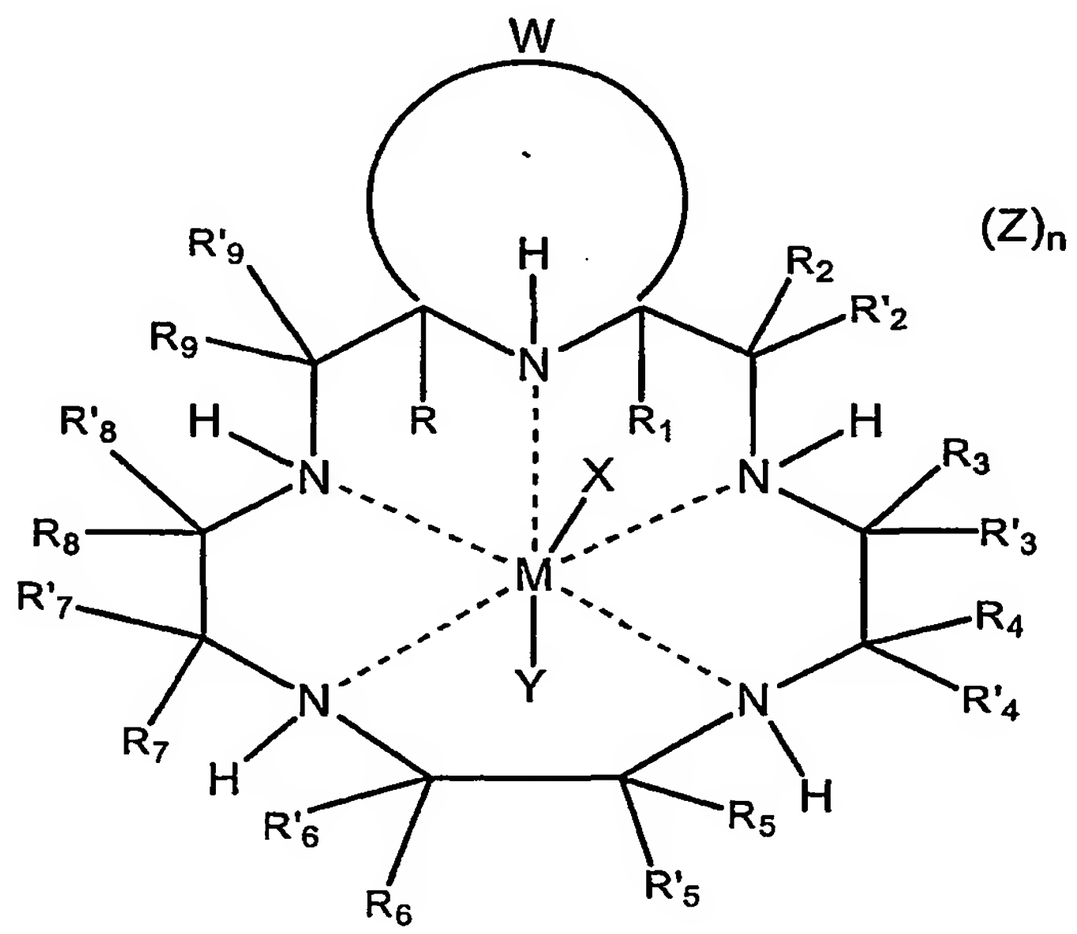
$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations thereof;

and wherein X, Y and Z are independently selected from the group consisting of halide, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), aryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous

acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins.

26. The method of claim 24 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula: .



wherein a nitrogen of the macrocycle and the two adjacent carbon atoms to which it is attached independently form a substituted, unsaturated, nitrogen-containing heterocycle W having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and wherein R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; and, optionally, one or more of R_2 or R'_2 and R_3 or R'_3,

R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, or R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and, optionally, one or more of R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and, optionally, one of R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R_1,, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x\text{-}M\text{-}(CH_2)_w\text{-}L\text{-}(CH_2)_z\text{-}I\text{-}(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations of any of the above; wherein M is a cation of a transition metal selected from the group consisting of manganese and iron; and wherein X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof.

27. The substituted pentaaza-macrocyclic ligand complex of claim 26 wherein U and V are trans-cyclohexanyl fused rings.

28. The substituted pentaaza-macrocyclic ligand complex of claim 26 wherein W is a substituted pyridino moiety.

29. The substituted pentaaza-macrocyclic ligand complex of claim 26 wherein U and V are trans-cyclohexanyl fused rings and W is a substituted pyridino moiety.

30. The method of claim 20 wherein the subject is a mammal.

31. The method of claim 30 wherein the mammal is a human.

32. A method for treatment of gliosis, the method comprising administering to a subject a therapeutically, prophylactically, pathologically or resuscitative effective amount of a composition comprising a catalyst for the dismutation of superoxide anions.

33. A method of claim 32 wherein treatment of gliosis is achieved by inhibiting oxidative stress of the components of neurons.

34. A method of claim 33 wherein the oxidative stress is mediated by superoxide anions.

35. The method of claim 34 wherein the neurons are dopaminergic neurons.

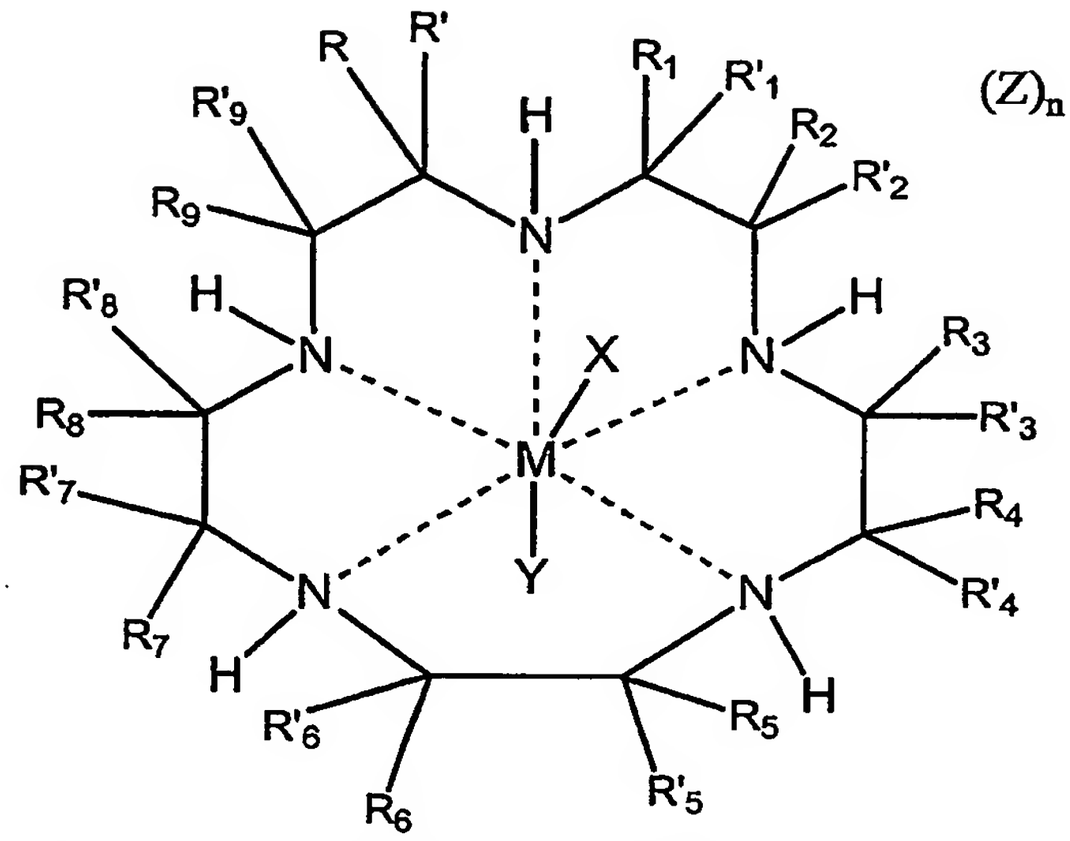
36. The method of claim 32 wherein treatment of gliosis is achieved by limiting neural cell death.

37. The method of claim 36 wherein the neural cell death is limited by preventing oxidative stress mediated by superoxide anions.

38. The method of claim 32 wherein the catalyst is a non-proteinaceous catalyst comprising an organic ligand chelated to a metal ion selected from the group of manganese(II), manganese(III), iron(II) and iron(III).

39. The method of claim 38 wherein the catalyst is a pentaaza-macrocyclic ligand complex or a substituted pentaaza-macrocyclic ligand complex.

40. The method of claim 39 wherein the pentaaza-macrocyclic ligand complex is represented by the following formula:



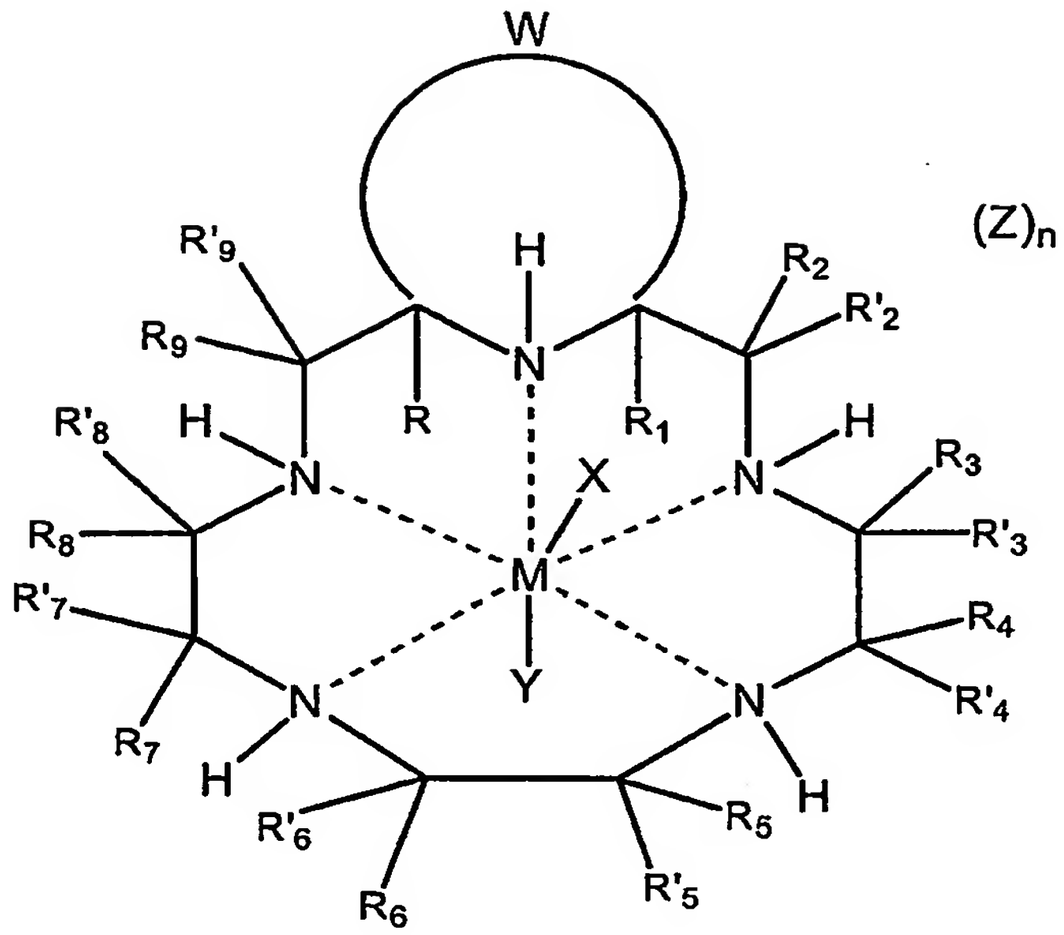
wherein M is a cation of a transition metal, preferably manganese or iron; wherein R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; R_1 or R'_1 and R_2 or R'_2, R_3 or R'_3 and R_4 or R'_4, R_5 or R'_5 and R_6 or R'_6, R_7 or R'_7 and R_8 or R'_8, and R_9 or R'_9 and R or R' together with the carbon atoms to which they are attached independently form a substituted or unsubstituted, saturated, partially saturated or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; R or R' and R_1 or R'_1, R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, and R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, provided that when the nitrogen containing heterocycle is an aromatic heterocycle which does not contain a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen as shown in the above formula, which nitrogen is also in the macrocyclic ligand or complex, and the R groups attached to the included carbon atoms of the macrocycle are absent; R and R', R_1 and R'_1, R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms; and one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R', R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations thereof;

and wherein X, Y and Z are independently selected from the group consisting of halide, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid (such as acetic acid, trifluoroacetic acid, oxalic acid), aryl carboxylic acid (such as benzoic acid, phthalic acid), urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkyl aryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins.

41. The method of claim 39 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:



wherein a nitrogen of the macrocycle and the two adjacent carbon atoms to which it is attached independently form a substituted, unsaturated, nitrogen-containing heterocycle W having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and wherein R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 independently represent hydrogen, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, alkylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals; and, optionally, one or more of R_2 or R'_2 and R_3 or R'_3, R_4 or R'_4 and R_5 or R'_5, R_6 or R'_6 and R_7 or R'_7, or R_8 or R'_8 and R_9 or R'_9 together with the carbon atoms to which they are attached independently form a substituted or unsubstituted nitrogen containing heterocycle having 2 to 20 carbon atoms, which may be an aromatic heterocycle, in which case the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and the R groups attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; and, optionally, one or more of R_2 and R'_2, R_3 and R'_3, R_4 and R'_4, R_5 and R'_5, R_6 and R'_6, R_7 and R'_7, R_8 and R'_8, and R_9 and R'_9, together with the carbon atom to which they are attached independently form a saturated, partially saturated, or unsaturated cyclic or heterocyclic having 3 to 20 carbon atoms;

and, optionally, one of R, R_1, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 together with a different one of R, R_1,, R_2, R'_2, R_3, R'_3, R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7, R'_7, R_8, R'_8, R_9, and R'_9 which is attached to a different carbon atom in the macrocyclic ligand may be bound to form a strap represented by the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-I-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and I are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, alkaryl, alkheteroaryl, aza, amide, ammonium, oxa, thia, sulfonyl, sulfinyl, sulfonamide, phosphoryl, phosphinyl, phosphino, phosphonium, keto, ester, alcohol, carbamate, urea, thiocarbonyl, borates, boranes, boraza, silyl, siloxy, silaza and combinations thereof; and combinations of any of the above; wherein M is a cation of a transition metal selected from the group consisting of manganese and iron; and wherein X, Y and Z represent suitable ligands or charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof.

42. The substituted pentaaza-macrocyclic ligand complex of claim 41 wherein U and V are trans-cyclohexanyl fused rings.

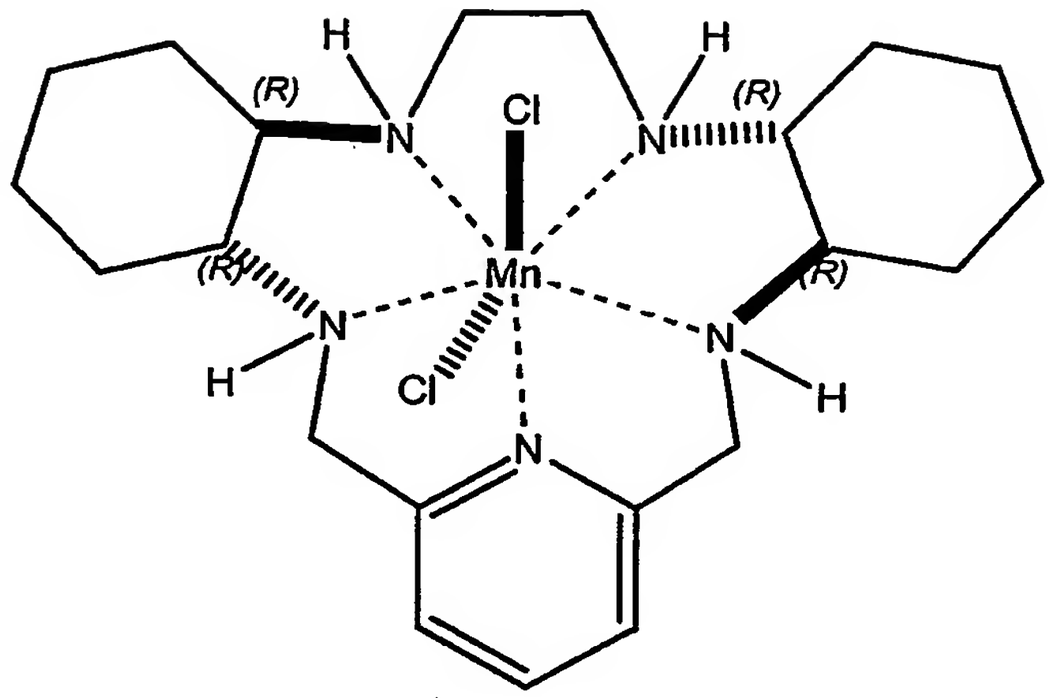
43. The substituted pentaaza-macrocyclic ligand complex of claim 41 wherein W is a substituted pyridino moiety.

44. The substituted pentaaza-macrocyclic ligand complex of claim 41 wherein U and V are trans-cyclohexanyl fused rings and W is a substituted pyridino moiety.

45. The method of claim 32 wherein the subject is a mammal.

46. The method of claim 45 wherein the mammal is a human.

47. A method of claim 39 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:



48. A method of claim 39 wherein the substituted pentaaza-macrocyclic ligand complex is represented by the following formula:

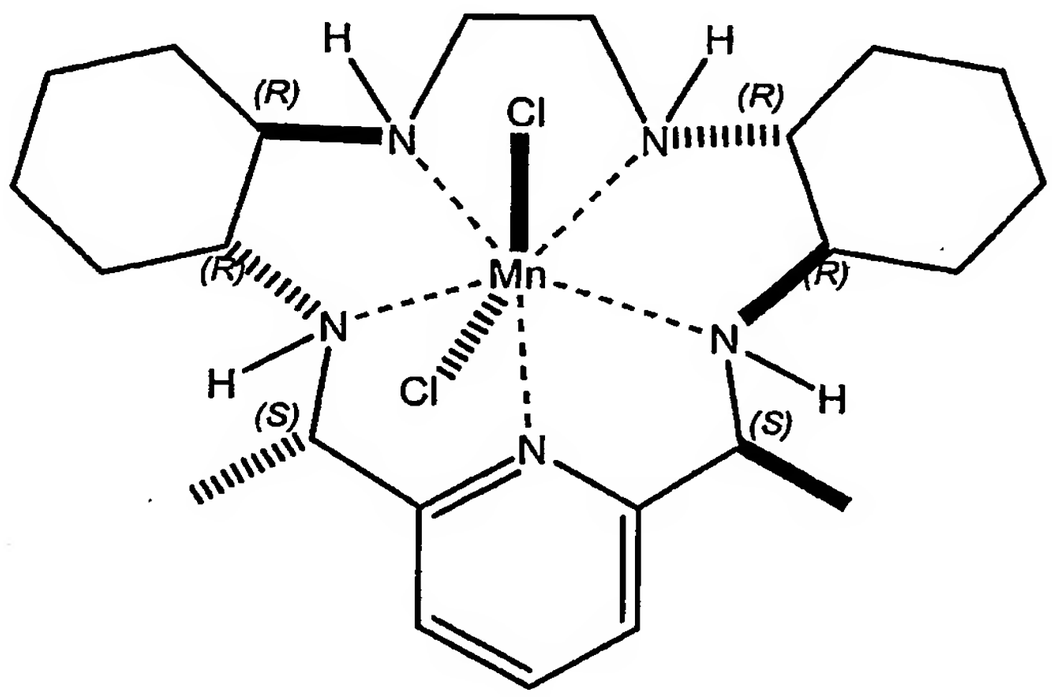


FIG. 1a

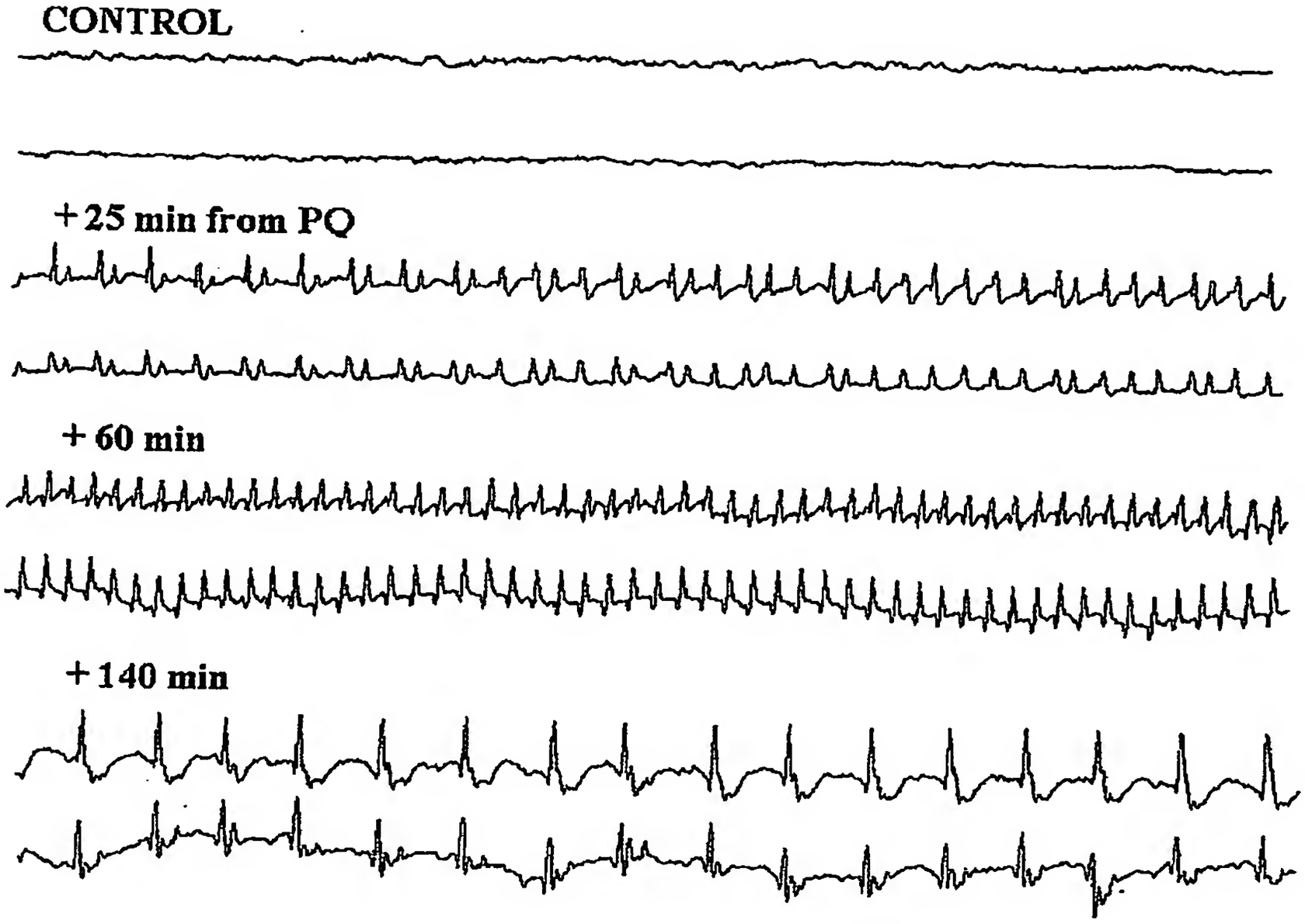


FIG. 1b

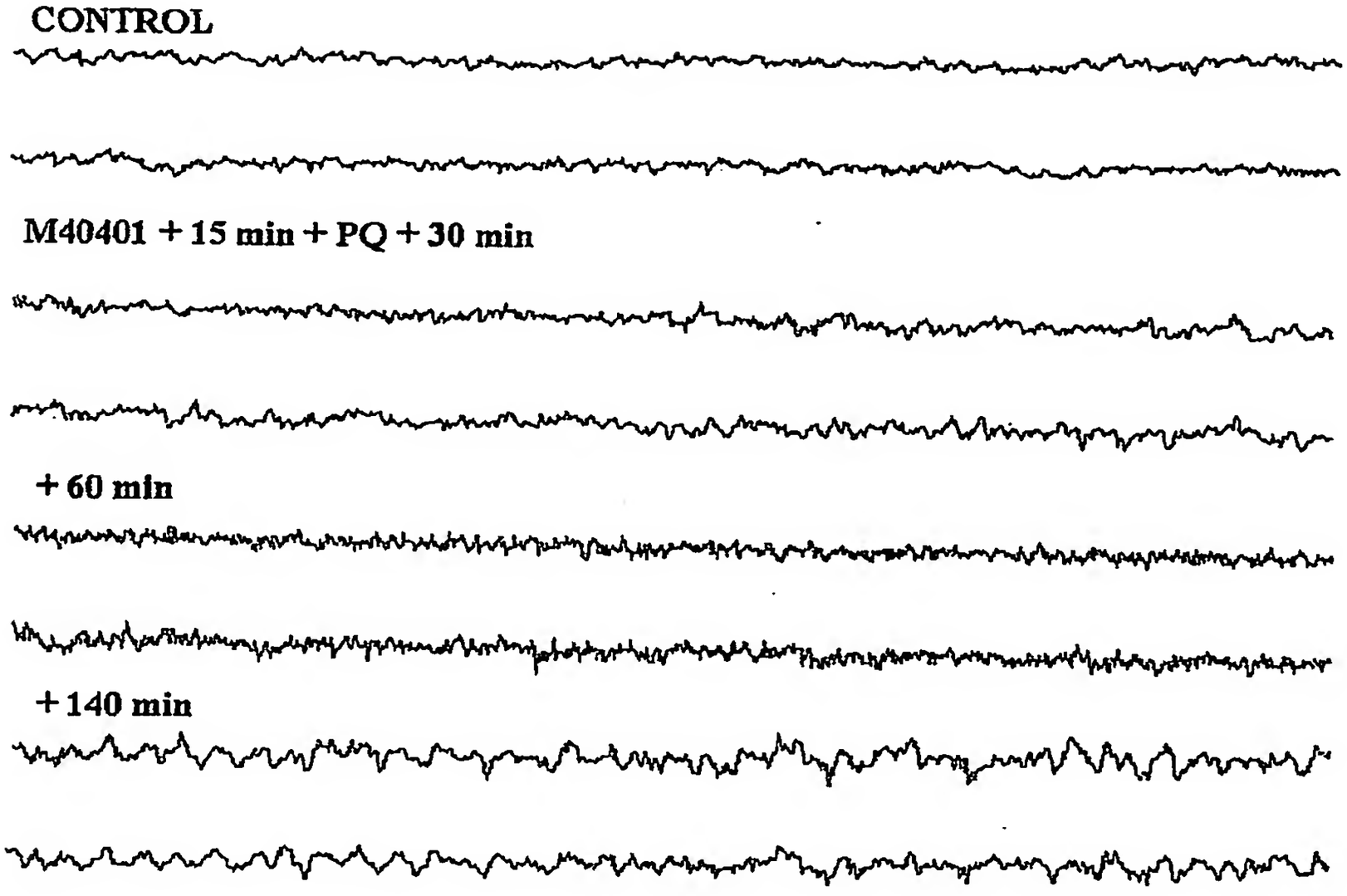
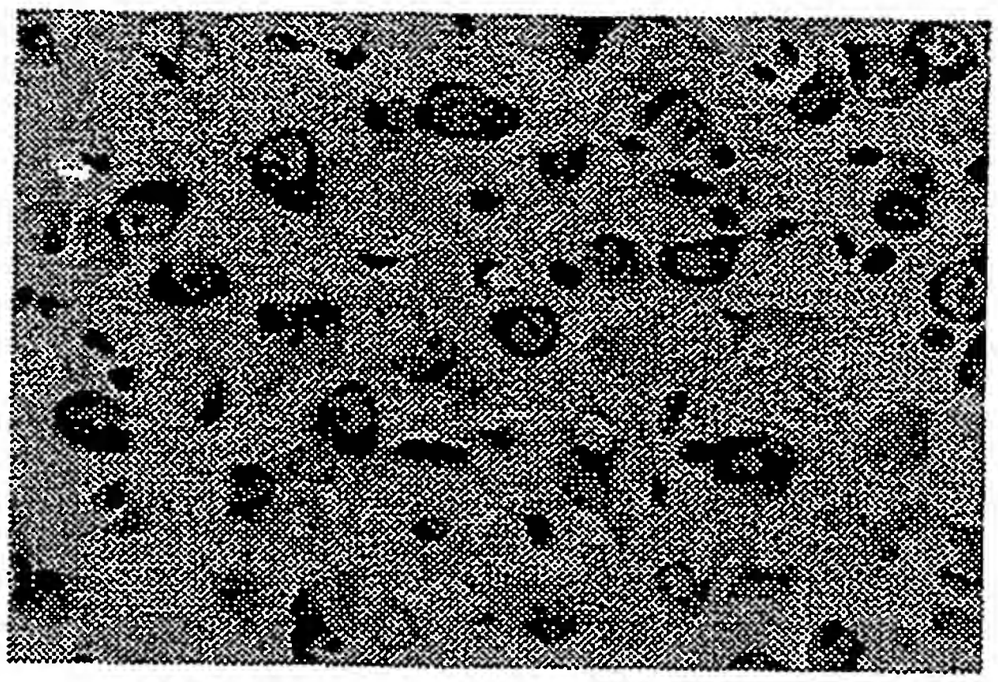
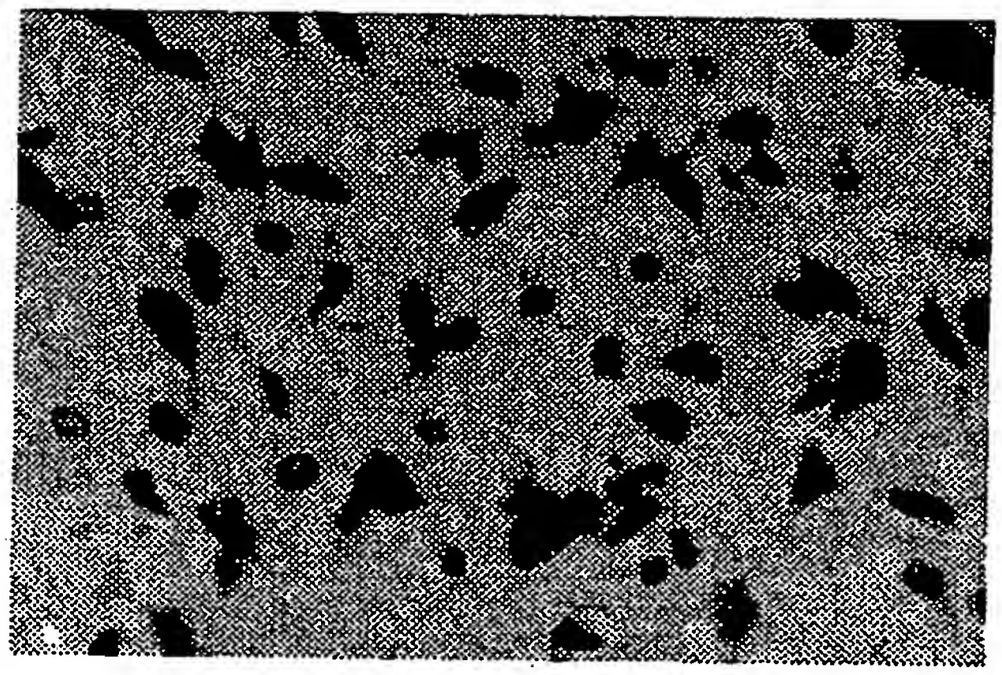


FIG. 2

A



B



C